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Author contributions

JK designed the study. JK and YM collected data. JK performed most statistical analyses and wrote the initial draft of the manuscript. AS, SF, and MA critically reviewed the manuscript. All authors have read and approved the final version of the manuscript.

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Abstract

Background: Osteoradionecrosis of the jaw (ORN) is a refractory late complication of radiation therapy. Radiation-induced fibrosis (RIF) is the most likely mechanism for developing ORN, and statins are effective against RIF. However, no reports have indicated the direct effectiveness of statins in treating ORN.

Purpose: This study aimed to measure the association between statin exposure and ORN disease resolution.

Study design, setting, sample: This retrospective cohort study included patients with ORN diagnosed between January 2008 and December 2020 at the Hospital's Department of Oral and Maxillofacial Surgery. Patients who were immunocompromised or followed up for < 6 months were excluded.

Predictor variable: The predictor variable was statin exposure, which was defined as the use of statins for dyslipidemia by coincidence.

Main outcome variable: The main outcome variable was ORN disease progression status (good prognosis). Patients who showed full recovery and improvement were included in the good prognosis group, and those who showed invariance and deterioration were included in the poor prognosis group.

Covariates: We analyzed the clinicodemographic including the age of onset, sex, history of smoking, alcohol consumption, history of chemotherapy, tumor site, association with dental treatment, location (maxilla or mandible), the time to ORN onset from radiation therapy, and stage of ORN, and treatment characteristics including hyperbaric oxygen therapy, long-term macrolide administration, and sequestrectomy.

Analyses: We analyzed the association between statin exposure/covariates and time to ORN improvement using bivariate and multivariate Cox regression. The significance level was set at $p = 0.05$.

Results: We analyzed 102 patients, and the improvement rate was 32.4%. The favorable prognostic factors were statin exposure (adjusted hazard ratio [HR], 3.71; 95% confidence interval [CI], 1.62–8.50; $p = 0.002$), onset in the maxilla (HR, 2.15; 95% CI, 1.02–4.55; $p = 0.045$), and stage 1 of ORN (HR, 2.65; 95% CI, 1.20–5.83; $p = 0.016$).

Conclusions and Relevance: In this study, statin exposure, onset in the maxilla, and stage 1 of Lyons's classification were favorable prognostic factors for ORN. Statins may be a novel and effective treatment for ORN.

Keywords*:* Hyperbaric oxygen therapy; Maxilla; Osteoradionecrosis; Radiation-induced fibrosis; Statin

Introduction

Radiation therapy (RT) is a major treatment strategy for head and neck cancer. Approximately 20.0% (0.9–35.0%) of patients receive RT during head and neck cancer treatment.[1] Osteoradionecrosis of the jaw (ORN) is an established refractory late complication, with a recently estimated incidence rate of 4–8%.[2-4] Notably, the hypoxic-hypocellular-hypovascular and radiation-induced fibrosis (RIF) theories have been largely accepted,[5,6] but the exact pathogenesis of ORN remains unclear. These theories form the cornerstone of hyperbaric oxygen therapy (HBO) and pentoxifylline-tocopherol (PENTO) therapy for ORN. [5,6]

Currently, there are no established ORN treatment. Conservative treatment, such as continuous antimicrobials and irrigation, is the primary approach; however, it may ultimately lead to jawbone resection, including mandibulectomy.[7] Reportedly, HBO is effective for treating ORN;[8] however, there are contradictory reports,[9] and a recent randomized controlled trial has questioned its efficacy.[10] Similarly, the efficacy of PENTO therapy has been recently reported;[11-13] a systematic review and meta-analysis estimated that 62.7% of the patients recovered fully or showed significant improvement without further therapeutic intervention for ORN.[14] Ongoing research suggests that PENTOCLO therapy (combining clodoronate with PENTO), maybe even more effective.[7]

Recently, the efficacy of statins against radiation-induced damage, including RIF, in various tissues has been reported in vitro and in vivo.[15-17] Statins are 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors that are safe and used globally for treating dyslipidemia. Statins are antifibrotic agents, and a 12-month therapy of statins is efficacious against radiation-induced cutaneous and subcutaneous fibrosis of the head and neck region.[18] To date, no reports have indicated the direct effectiveness of statins in treating ORN.

Based on pathophysiological considerations, we hypothesized that ORN is caused by RIF and statins are effective in improving ORN. More conservative treatment options may increase the possibility of avoiding mandibulectomy. In this study, we aimed to measure the association between statin exposure and ORN disease resolution. Consequently, we retrospectively selected factors associated with ORN prognosis to examine whether statins were relevant prognostic factors.

Materials and Methods

STUDY DESIGN/SAMPLE

The investigators designed and implemented a retrospective cohort study to address the purpose of this research. The study population comprised all patients with ORN diagnosed between January 2008 and December 2020 at the Hospital's Department of Oral and

Maxillofacial Surgery. This study was independently reviewed and approved by the ethics committee of Kobe University Hospital (certificate no. B210248) and was conducted in accordance with the Declaration of Helsinki. If information relevant to the study was disclosed and the eligible patients did not offer to opt-out, implied consent was assumed to have been obtained. Since there was no opt-out offer from the eligible patients in this study, informed consent was considered obtained from all patients. According to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE ver. 5),[19] ORN is classified briefly into grade 1: asymptomatic; clinical or diagnostic observations only; intervention not indicated; grade 2: symptomatic; medical intervention indicated; limitations in the performance of instrumental activities of daily living (ADL); grade 3: severe symptoms; limitations in the performance of self-care ADL; elective operative intervention indicated; grade 4: life-threatening consequences; urgent intervention indicated; and grade 5: death. The inclusion criteria were as follows: the diagnosis of, devitalization and exposure of bone through the overlying mucosa within the irradiated area (grade ≥ 2, CTCAE ver. 5), and persisting without healing for 3 months in the absence of tumor recurrence.[3,20] The exclusion criteria were: (1) immunocompromised status, such as the use of immunosuppressive drugs, including anticancer drugs; (2) cachexia with tumor; (3) a follow-up period of < 6 months, and (4) an unknown RT dose.

VARIABLES

The predictor variable was statin exposure. Statin users had been taking them for dyslipidemia by coincidence.

The primary outcome was disease improvement. We also assessed the time between irradiation and ORN onset. We divided the disease progression status of ORN into four categories: (i) full recovery: complete healing; (ii) improvement: improvement in symptoms, reduction in the extent of bone exposure, dermal fistula disappearance, and bone growth on radiographs; (iii) invariance: no improvement in symptoms or exacerbation of symptoms; (iv) deterioration: worsening of symptoms, increased bone exposure, the appearance of cutaneous fistulas, pathological fractures, increased bone resorption, and bone destruction on radiographs. We assessed the outcome by comparing the patient's health status differences at ORN diagnosis and the last follow-up examination. Furthermore, the patients were divided into two groups: the good prognosis group, showing full recovery and improvement and the poor prognosis group, showing invariance and deterioration. Patients who underwent mandibulectomy were classified under poor prognosis ("deterioration" group) regardless of their subsequent course because this study focused on the course of conservative treatment. In the case of mandibulectomy, the follow-up period was defined as the time from diagnosis to surgery.

Covariates comprised clinicodemographic and treatment characteristics. Patients' clinicodemographic included the age of onset, sex, history of smoking, alcohol consumption, history of chemotherapy, RT technique, total dose (Gy), tumor site, the association with dental treatment, location (maxilla or mandible), duration from the start of RT to ORN onset, and stage of ORN. Treatment characteristics included HBO, long-term macrolide administration, statin use, sequestrectomy, and mandibulectomy (with or without reconstruction). Lyon's classification for ORN staging was applied:[21] stage 1, affected (damaged or exposed) bone < 2.5 cm; stage 2, affected bone > 2.5 cm, asymptomatic; stage 3, affected bone > 2.5 cm, symptomatic; and stage 4, affected bone with pathological fracture, orocutaneous fistula, or involvement of the inferior alveolar nerve. Sequestrectomy was performed if the sequestrum was completely separated.

DATA COLLECTION METHODS

We reviewed the study subjects' electronic health records for the demographics and operative variables and stored them in a secure database in accordance with the guidelines for handling personal information at Kobe University to ensure that their identities were protected.

DATA ANALYSES

The representative value was the median with range or first and third quartile points. Nominal and continuous variables were compared between the groups using Fisher's exact test and the Brunner–Munzel test, respectively. Unadjusted hazard ratios (HR) were calculated using Cox

regression analysis between statin exposure/covariates and prognostic improvement of ORN. We analyzed the ORN improvement estimate using the Kaplan–Meier survival analysis. The log–rank test was performed to compare both groups. Similarly, the time to ORN onset after RT was analyzed with Kaplan–Meier analysis, and dyslipidemia among treatments with Bonferroni correction were compared using the log–rank test. In the multivariate Cox regression model to calculate the adjusted HR, we included statin exposure as a predictor, HBO as previously validated for ORN, and variables associated with good prognosis in univariate analyses. The significance level was set at $p = 0.05$. Statistical analysis was performed using R software version 3.4.1 (R Development Core Team, 2017; R Foundation for Statistical Computing, Austria).

Results

Of the 117 patients diagnosed with ORN, 15 were excluded, while 102 met the inclusion criteria (Fig. 1). The participant number was assigned based on the affected site. Therefore, in cases where one patient had multiple affected sites, each affected site was analyzed separately. No patient had a history of bisphosphonate or denosmab use. All patients were treated with antimicrobials and local irrigation. The median age of the patients was 68 years; most were male, and most had a history of chemotherapy. The most common tumor site was the oropharynx, followed by the oral cavity. The location of onset was mostly in the mandible

(83.3%). The median time to onset was 4.4 years from RT. HBO, sequestrectomy, and mandibulectomy were performed in eight (7.8%), 46 (45.1%), and 27 (26.5%) patients, respectively. All patients who underwent mandibulectomy had no ORN recurrence. In total, 12 patients had been prescribed statins, and all of them had been taking them for dyslipidemia before ORN onset (before RT, 8 patients; after RT, 4 patients). The statins used were rosuvastatin (2.5 mg once daily, n = 4), atorvastatin (10 mg once daily, n = 4), and pitavastatin (1 mg once daily, n = 4). All the medications are strong statins and were taken at standard doses. The exact duration of statin use was unknown; however, the median duration from the start of statin use to the onset of ORN was at least 52 (range, 7–132) months and from the start of statin use to recovery or improvement was 78 (range, 12–162) months. The respective values for frequency and median (range) follow-up period of each outcome were 20.6% and 35 (6–166) months for full recovery, 11.8% and 44 (6–117) months for improvement, 31.4% and 25 (6–132) months for invariance, and 36.3% and 18 (6–128) months for deterioration ($p = 0.073$) (Table 1).

Bivariate analyses of covariates versus statin exposure revealed a significant difference in the time to ORN onset from RT ($p = 0.003$) (Table 2).

We observed a good prognosis in 33 patients (32.4%). The covariates associated with improved prognosis in ORNs were onset in the maxilla (unadjusted HR 2.81, 95% CI 1.36–5.80, $p = 0.005$) and stage 1 of ORN (unadjusted HR 2.87, 95% CI 1.35–6.07, $p =$

0.006) (Table 3). HBO was not significantly associated with improved prognosis. In addition, statin exposure, the predictor variable, was significantly associated with improved prognosis (unadjusted HR 3.16, 95% CI 1.41–7.06, $p = 0.005$) (Table 4) (Fig. 2). Of the Statin users, eight (66.7%) had a good prognosis. There were five statin users with stage 1, two with stage 2, one with stage 3, and four with stage 4 ORN, of which all statin users with a poor prognosis had stage 4 ORN.

Multivariate analysis was performed with statin exposure as an explanatory variable in addition to HBO, onset in the maxilla, and stage 1 of ORN. Multivariate Cox regression analysis of favorable prognostic factors showed significant differences in statin exposure (adjusted HR 3.71, 95% CI 1.62–8.50, $p = 0.002$), onset in the maxilla (adjusted HR 2.15, 95% CI 1.02–4.55, $p = 0.045$), and stage 1 of ORN (adjusted HR 2.65, 95% CI 1.20–5.83, $p = 0.016$) (Table 5).

In total, 22 patients were treated for dyslipidemia. Of the 10 non-statin users with dyslipidemia, 2 patients used ezetimibe and bezafibrate and 6 patients underwent diet and exercise therapy. In the time to ORN onset from RT, patients without dyslipidemia had the earliest onset, followed by patients with non-statin treatment and patients with statin treatment (median [95% CI], 46.5 [30–54] months; 96 [43–119] months; 100 [35–137] months, $p = 0.001$). Among them, we observed a significant difference between patients with statin treatment and patients without dyslipidemia ($p = 0.006$) (Fig. 3).

Discussion

Currently, the RIF theory is the most promising pathology for ORN. We hypothesized that statins with antifibrotic properties effectively improve the disease state of ORN. In this study, we aimed to measure the association between statin exposure and ORN disease resolution.

In this study, statin exposure improved the prognosis by approximately 4-fold. This study's findings support our hypothesis that statins are a favorable prognostic factor for ORN. All patients were taking statins before the onset of ORN, suggesting that statin therapy for ORN would be more useful for treatment rather than prevention. To our knowledge, this is the first report on this finding. In addition, disease onset in the maxilla and stage 1 of ORN are more likely to improve (adjusted HR 2.15, 2.65, respectively), although onset in the maxilla was less likely to develop. In this study, HBO had a poor impact on ORN improvement.

Statins inhibit HMG-CoA reductase in the mevalonate pathway, inhibiting cholesterol production and lowering low-density lipoprotein in the blood. Moreover, isoprenoids, such as geranylgeranyl pyrophosphate and farnesyl pyrophosphate, intermediate metabolites of the mevalonate pathway, are involved in the lipid modification of small guanosine 5'-triphosphate-binding proteins like Rab, Ras, Rho, and Rap. Many studies have reported the pleiotropic effects of statins by inhibiting this process or by statins

themselves.[22,23] The main pleiotropic effects of statins include angiogenesis;[24-26] immunomodulation, including anti-inflammatory effects;[27,28] antioxidant effects;[29,30] and activation of osteoblasts to promote osteogenesis.[31-33]

RIF involves a variety of responses, including radiation-induced microvascular damage, excessive production of reactive oxygen species (ROS), sustained inflammatory response (secretion of inflammatory cytokines), and increased production of transforming growth factor-beta1 (TGF-β1). Consequently, myofibroblasts differentiate and proliferate from fibroblasts, and fibrosis occurs because of prolonged formation and accumulation of extracellular matrix, without myofibroblast apoptosis, due to persistent abnormal stimulation. Damage to vascular endothelial cells, causing atherosclerosis, vascular occlusion, and secondary hypoxia, is also involved in RIF.[17] Reportedly, statins have in vivo effects on RIF, such as radiation-induced injury of the lungs, cardiovascular system, intestine, and kidney.[34-37] Primarily, statins effect on RIF include subduing the differentiation and proliferation of myofibroblasts by suppressing TGF-β1 through anti-inflammatory processes and ROS suppression.[17,38,39]

The RIF theory was proposed to explain ORN pathogenesis; statins are theoretically expected to be effective against ORN. Based on the present results, statins are effective against ORN. However, patients with compromised immune function, including patients having cachexia with tumors were excluded from this study; therefore, statins may be

effective for mild ORN with preserved immune function. The hypothesized mechanisms of action of statins in ORN are as follows: 1) anti-fibrosis by suppressing abnormal myofibroblasts, 2) anti-inflammatory effects, 3) angiogenesis, and 4) promotion of osteogenesis (Fig. 4).[6,17,24-33,38,39] Post-RT vasculopathy is a common adverse effect that causes fibrosis due to vascular damage, platelet aggregation, and inflammation.[40,41] Furthermore, head and neck RT has been associated with an increased risk of ischemic stroke, transient ischemic attack, carotid stenosis, and carotid injury after cervical irradiation.[42] Statins significantly reduce cardiovascular and cerebrovascular events after head and neck irradiation and improve radiation-induced cutaneous and subcutaneous fibrosis.[18,43] These findings suggest that statins could have an advantage against complications of RT in the head and neck region, including ORN. Though speculative, many patients with ORN are elderly, and atherosclerosis may be present even in the absence of dyslipidemia diagnosis. Consequently, the time until ORN onset may be prolonged since the general treatment of dyslipidemia somewhat improves peripheral vascular flow[44]. In particular, statins might have significantly delayed the onset of ORN.

In this study, HBO did not promote the healing of ORN. It was suggested that HBO had a poor ameliorative effect on ORN. Its effectiveness has been questioned recently.[10] However, few patients underwent HBO; therefore, this result needs careful interpretation.

Maxillary ORN occurs less frequently and is more easily cured than mandibular ORN.[45,46] The main cause is considered to be because the mandible has less blood supply than the maxilla and wound healing is less effective. Therefore, regarding anatomical structure and function, maxillary ORN remains stable indefinitely .[46,47] Maxillary ORN has a healing rate of 82.5% and 85.7% with treatment by HBO.[46,48] This study's findings support previous reports that onset in the maxilla is a likely favorable prognostic factor.

In this study, long-term macrolide administration was considered a treatment-related factor because macrolides have immunomodulatory and TGF-β1 suppressive effects.[49,50] However, long-term macrolide administration was not associated with ORN prognosis in this study. As there are no reports on the effectiveness of long-term macrolide therapy in ORN, we believe that the present results are reasonable.

This study has some limitations. First, observer and recorder biases might have been introduced during data collection due to the retrospective design. In addition, there might be a risk of timing bias. Second, the reliability of the results was slightly low due to the small sample size. Third, the local dose may reflect the effectiveness of RT for ORN more strongly than the total dose. However, the total dose was used in this study due to missing data. Fourth, the present study has a strong qualitative aspect for evaluating ORN, and few quantitative evaluations have been performed. Specifically, it is necessary to evaluate how the effect manifests depending on the severity of the disease. Furthermore, the extent of bone

formation must be evaluated using computed tomography. Fifth, patients with immunosuppressive status were not included because this study focused on conservative treatment for patients without immunosuppression. Therefore, caution is needed in interpreting this study's results. However, we believe that this study will serve as a stepping stone in developing new treatments for ORN. Considering these limitations, a prospective study on this topic is currently planned as a clinical trial, including whether statins have a preventive effect on ORN and how long statins should be administered.

Conclusions

In this study, factors that promoted ORN improvement were statin exposure, onset in the maxilla, and stage 1 of ORN. Statins may also have an additive effect on post-RT complications as they reportedly reduce radiation-induced cutaneous fibrosis and cardiovascular and cerebrovascular events after head and neck RT. This study's findings were insufficient to recommend statin use for ORN. However, statins might be a new, simple, and safe medical option for treating ORN, including other complications after head and neck RT.

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Tables

Table 1. Patient and treatment characteristics

Variables	Number of patients (n = 102)
Patient characteristics	
Age (years)	68 (63, 76)
Sex (male)	86 (84.3%)
History of smoking (yes)	50 (49.0%)
Alcohol consumption (yes)	53 (52.0%)
History of chemotherapy (yes)	80 (78.4%)
RT technique	
3D-CRT	87 (85.3%)
IMRT	14 (13.7%)
Heave particles irradiation	1 (1.0%)
Total dose (Gy)	66 (66, 70)
Tumor site	
Oral cancer	39 (38.2%)
Nasopharyngeal cancer	6 (5.9%)
Oropharyngeal cancer	40 (39.2%)
Hypopharyngeal cancer	6 (5.9%)

Salivary gland cancer	3 (2.9%)
CUP	8 (7.8%)
Associated with dental treatment (yes)	33 (32.4%)
Location	
Maxilla	17 (16.7%)
Mandible	85 (83.3%)
Duration from RT (months)	53 (25, 86)
Stage of ORN	
Stage 1	51 (50.0%)
Stage 2	5 (4.9%)
Stage 3	3 (2.9%)
Stage 4	43 (42.2%)
Treatment characteristics	
HBO	8 (7.8%)
Macrolides	31 (30.4%)
Statins	12 (11.8%)
Sequestrectomy	46 (45.1%)
Mandibulectomy	27 (26.5%)
Outcome	

Full recovery	21 (20.6%)
Improvement	12 (11.8%)
Invariance	32 (31.4%)
Deterioration	37 (36.3%)
Follow-up duration (months)	25 (12, 45)

Data are shown as the median (first quartile, third quartile) or n (%).

Abbreviations: 3D-CRT, three-dimensional conformal radiation therapy; CUP, cervical lymph node metastasis from an unknown primary site; HBO, hyperbaric oxygen therapy; IMRT, intensity-modulated radiation therapy; ORN, osteoradionecrosis of the jaw; RT, radiation therapy

Table 2 Bivariate analyses of covariates versus predictor variable, statin exposure

Covariates	Predictor variable (statin exposure)		
	Yes (n = 12)	No (n = 89)	*p*-value
Age (years)	71 (68, 72)	68 (62, 76)	.325
Sex (male)	4 (33.3%)	12 (13.3%)	.092
History of smoking (yes)	3 (25.0%)	47 (52.2%)	.123
Alcohol consumption (yes)	4 (33.3%)	49 (54.4%)	.223
History of chemotherapy (yes)	9 (75.0%)	71 (78.9%)	.718
Tumor site			.797
Oral cancer	4 (33.3%)	36 (40.0%)	
Nasopharyngeal cancer	0	6 (6.7%)	
Oropharyngeal cancer	7 (58.3%)	33 (36.7%)	
Hypopharyngeal cancer	0	6 (6.7%)	
Salivary gland cancer	0	2 (2.2%)	
CUP	1 (8.3%)	7 (7.8%)	
Associated with dental treatment (yes)	4 (33.3%)	29 (32.2%)	1.000
Location (Maxilla)	3 (25.0%)	14 (15.6%)	.417
Duration from RT (months)	**100 (71, 133)**	**50 (22, 81)**	**.005***

Stage of ORN			.111
Stage 1	5 (41.7%)	46 (51.1%)	
Stage 2	2 (16.7%)	3 (3.3%)	
Stage 3	1 (8.3%)	2 (2.2%)	
Stage 4	4 (33.3%)	39 (43.3%)	
HBO (yes)	1 (8.3%)	7 (7.8%)	1.000
Macrolide (yes)	2 (16.7%)	29 (32.2%)	.337
Sequestrectomy (yes)	8 (66.7%)	38 (42.2%)	.132

Data are shown as the median (first quartile, third quartile) or n (%).

* Statistically significant ($p < 0.05$).

Abbreviations: CUP, cervical lymph node metastasis from an unknown primary site; HBO, hyperbaric oxygen therapy; ORN, osteoradionecrosis of the jaw; RT, radiation therapy

Table 3. Bivariate analyses of covariates versus outcome variable, ORN disease progression status

Covariates	Outcome variable		
	Good prognosis (n = 33)	HR (95% CI)	*p*-value
Age (years)	67 (60, 71)	0.98 (0.96–1.01)	.233
Sex			
Male	28 (84.8%)	Reference	.709
Female	5 (15.2%)	0.83 (0.32–2.17)	
History of smoking			
No	18 (54.5%)	Reference	.603
Yes	15 (45.5%)	0.83 (0.42–1.66)	
Alcohol consumption			
No	19 (57.6%)	Reference	.082
Yes	14 (42.4%)	0.54 (0.27–1.08)	
History of chemotherapy			
No	9 (27.3%)	Reference	.369
Yes	24 (72.7%)	0.70 (0.32–1.52)	
Tumor site			

Oral cancer	18 (54.5%)	Reference	
Nasopharyngeal cancer	1 (3.0%)	0.44 (0.06–3.33)	.429
Oropharyngeal cancer	10 (30.3%)	0.54 (0.25–1.18)	.125
Hypopharyngeal cancer	2 (6.1%)	1.45 (0.33–6.48)	.624
Salivary gland cancer	1 (3.0%)	0.83 (0.11–6.24)	.855
CUP	1 (3.0%)	0.30 (0.04–2.29)	.248
Associated with dental treatment			
No	23 (69.7%)	Reference	.823
Yes	10 (30.3%)	0.92 (0.44–1.93)	
Location			
Mandible	22 (66.7%)	Reference	**.005***
Maxilla	11 (33.3%)	**2.81 (1.36–5.80)**	
Duration from RT (months)	100 (71, 133)	1.00 (0.99, 1.01)	.105
Stage of ORN			
Stage 1	23 (69.7%)	Reference	
Stage 2	2 (6.1%)	0.43 (0.10‑1.87)	.258
Stage 3	2 (6.1%)	1.03 (0.24–4.41)	.970
Stage 4	6 (18.2%	0.27 (0.11–0.67)	**.004***
HBO			

No	31 (93.9%)	Reference	.171
Yes	2 (6.1%)	0.36 (0.09–1.55)	
Macrolides			
No	25 (75.8%)	Reference	.151
Yes	8 (24.2%)	0.56 (0.25–1.24)	
Sequestrectomy			
No	9 (27.3%)	Reference	.052
Yes	24 (72.7%)	2.16 (0.99–4.69)	

Data are shown as the median (first quartile, third quartile) or n (%).

* Statistically significant ($p < 0.05$).

Abbreviations: CI, confidence interval; CUP, cervical lymph node metastasis from an unknown primary site; HBO, hyperbaric oxygen therapy; HR, hazard ratio; ORN, osteoradionecrosis of the jaw; RT, radiation therapy

Table 4. Bivariate analysis of predictor variable (statin exposure) versus outcome variable (disease progression status)

Predictor variable	Outcome variable		
	Good prognosis (n = 33)	HR (95% CI)	*p*-value
Statin exposure			
No	25 (75.8%)	Reference	**.005***
Yes	**8 (24.2%)**	**3.16 (1.41–7.06)**	

Data are shown as the n (%).

* Statistically significant ($p < 0.05$).

Abbreviations: CI, confidence interval; HR, hazard ratio

Table 5. Favorable prognostic factors for ORN: multivariate Cox regression analysis

Variables	Outcome variable (good prognosis)	
	Adjusted HR (95% CI)	*p*-value
Statin exposure		
No	Reference	**.002***
Yes	**3.71 (1.62–8.50)**	
HBO		
No	Reference	.222
Yes	0.40 (0.09–1.74)	
Location		
Mandible	Reference	**.045***
Maxilla	**2.15 (1.02–4.55)**	
Stage of ORN		
Non-stage 1	Reference	**.016***
Stage 1	**2.65 (1.20–5.83)**	

* Statistically significant ($p < 0.05$).

Abbreviations: CI, confidence interval; HBO, hyperbaric oxygen therapy; HR, hazard ratio risk; ORN, osteoradionecrosis of the jaw

Figure legends

Fig. 1. Flowchart and data cleaning

RT, radiation therapy

Fig. 2. Kaplan–Meier survival curve for improving of osteoradionecrosis of the jaw

(A) statin exposure, (B) HBO, (C) location of ORN onset, (D) stage of ORN.

ORN, osteoradionecrosis of the jaw; HBO, hyperbaric oxygen therapy

Fig. 3. Kaplan–Meier survival curve for the time to osteoradionecrosis of the jaw onset after radiation therapy to compare dyslipidemia among treatments

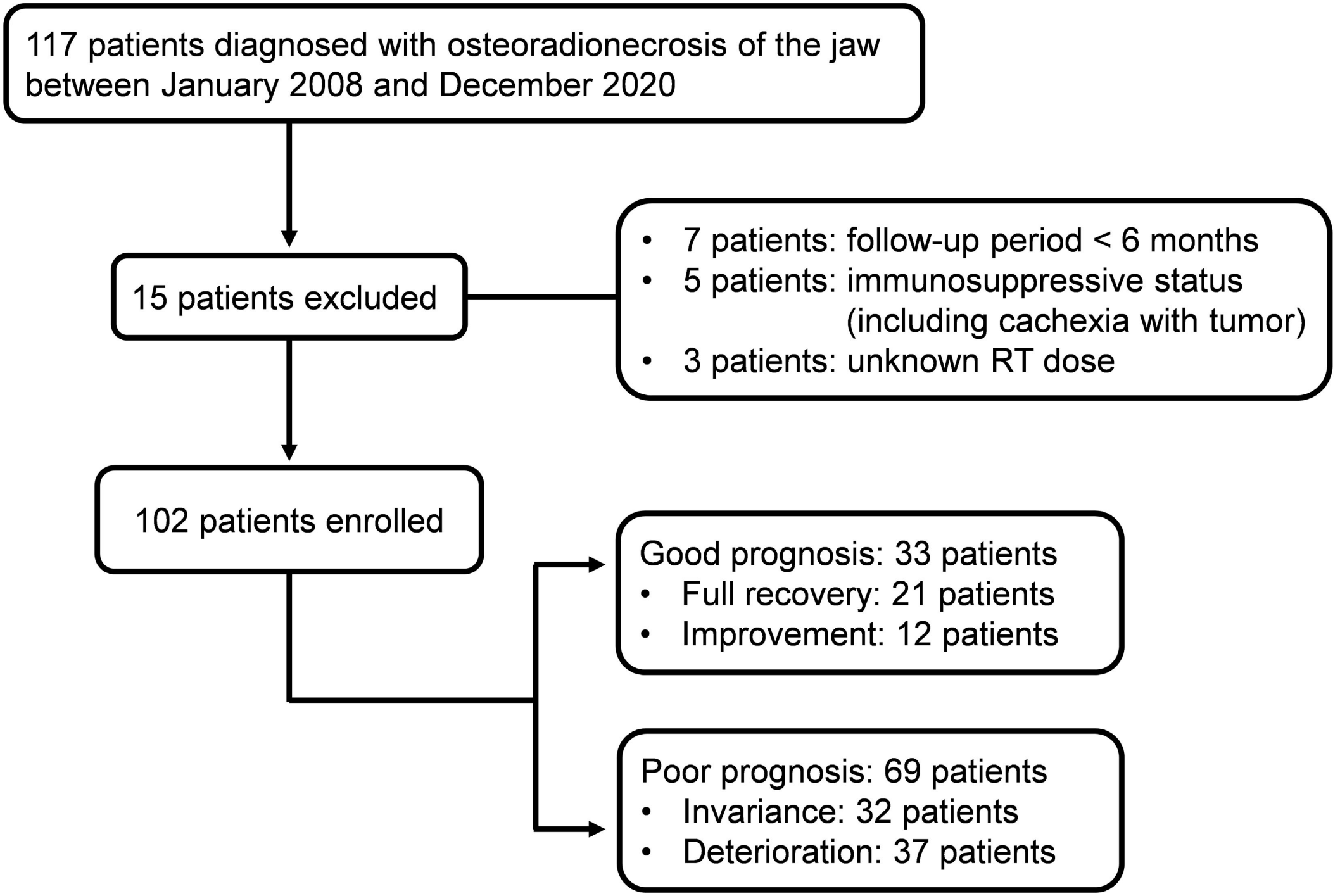
ORN, osteoradionecrosis of the jaw

Fig. 4. Hypothetical simplified graphical representation of the effect of statins on osteoradionecrosis of the jaw

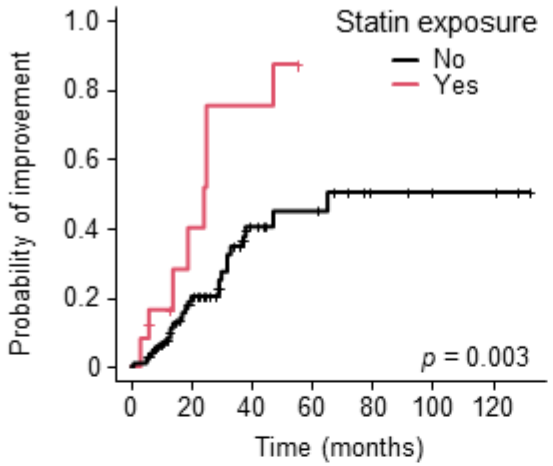
Irradiation can damage vascular endothelial cells, resulting in vascular injury. In addition, the inflammatory response and ROS produced by inflammatory cells result in TGF-β1 release. Further, radiation injury causes EMT/EndMT and inflammatory response, leading to fibroblast induction and proliferation. Excessive ROS and TGF-β1 induce differentiation of myofibroblasts from fibroblasts, resulting in abnormal formation and accumulation of the

extracellular matrix. In addition, bone-related cells, such as osteoblasts, are injured and transformed into fragile, non-cellular tissues. ORN develops as a result of trauma to the irradiated area (RIF theory). The possible effects of statins on ORN include (1) promoting endothelial function, (2) angiogenesis, (3) immunomodulation, (4) osteoblast activation, (5) anti-inflammatory effects, and (6) ROS inhibition. Consequently, it inhibits abnormal myofibroblasts and attenuates fibrosis. In addition, it promotes angiogenesis and activates osteoblasts, leading to wound healing.

ECM, extracellular matrix; EMT/EndMT, epithelial/endothelial to mesenchymal transition; ORN, osteoradionecrosis of the jaw; RIF, radiation-induced fibrosis; ROS, reactive oxygen species; TGF-β1, transforming growth factor-beta1

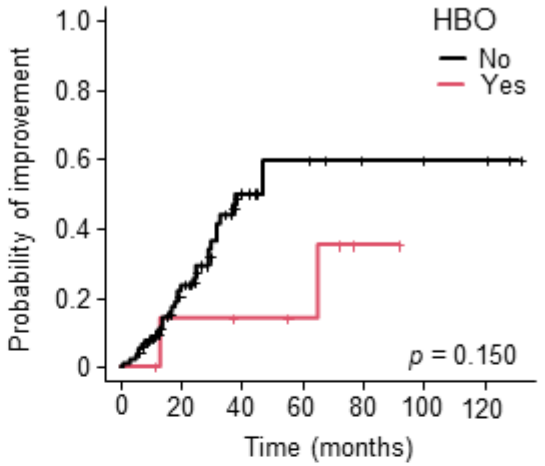

117 patients diagnosed with osteoradionecrosis of the jaw between January 2008 and December 2020
15 patients excluded
• 7 patients: follow-up period < 6 months
• 5 patients: immunosuppressive status (including cachexia with tumor)
• 3 patients: unknown RT dose
102 patients enrolled
Good prognosis: 33 patients
• Full recovery: 21 patients
• Improvement: 12 patients
Poor prognosis: 69 patients
• Invariance: 32 patients
• Deterioration: 37 patients

A



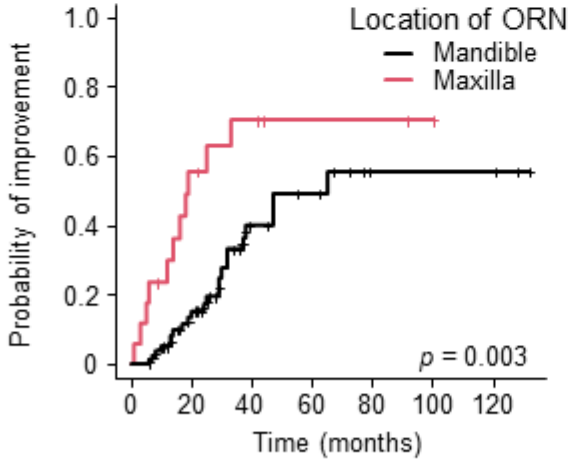
Number at risk							
No	90	48	17	12	5	4	3
Yes	12	5	2	0	0	0	0

B



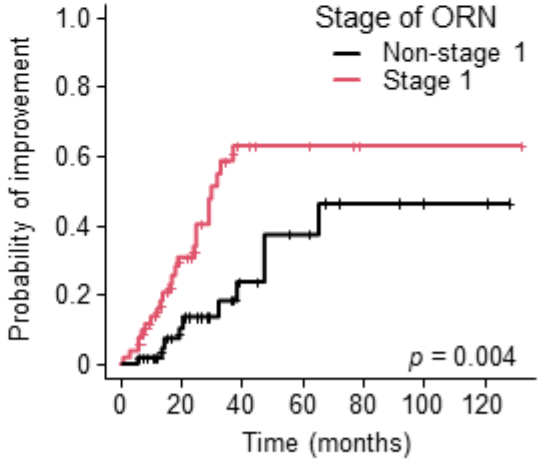
Number at risk							
No	94	47	14	8	4	4	3
Yes	8	6	5	4	1	0	0

C

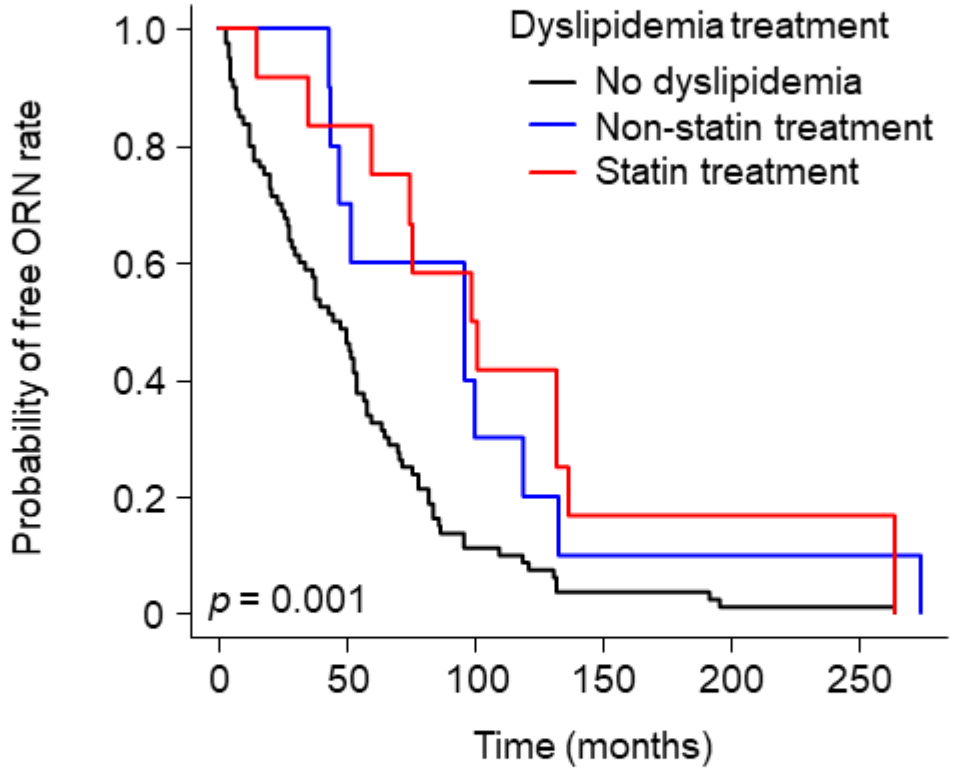


Number at risk							
Mandible	85	46	15	10	3	3	3
Maxilla	17	7	4	2	2	1	0

D

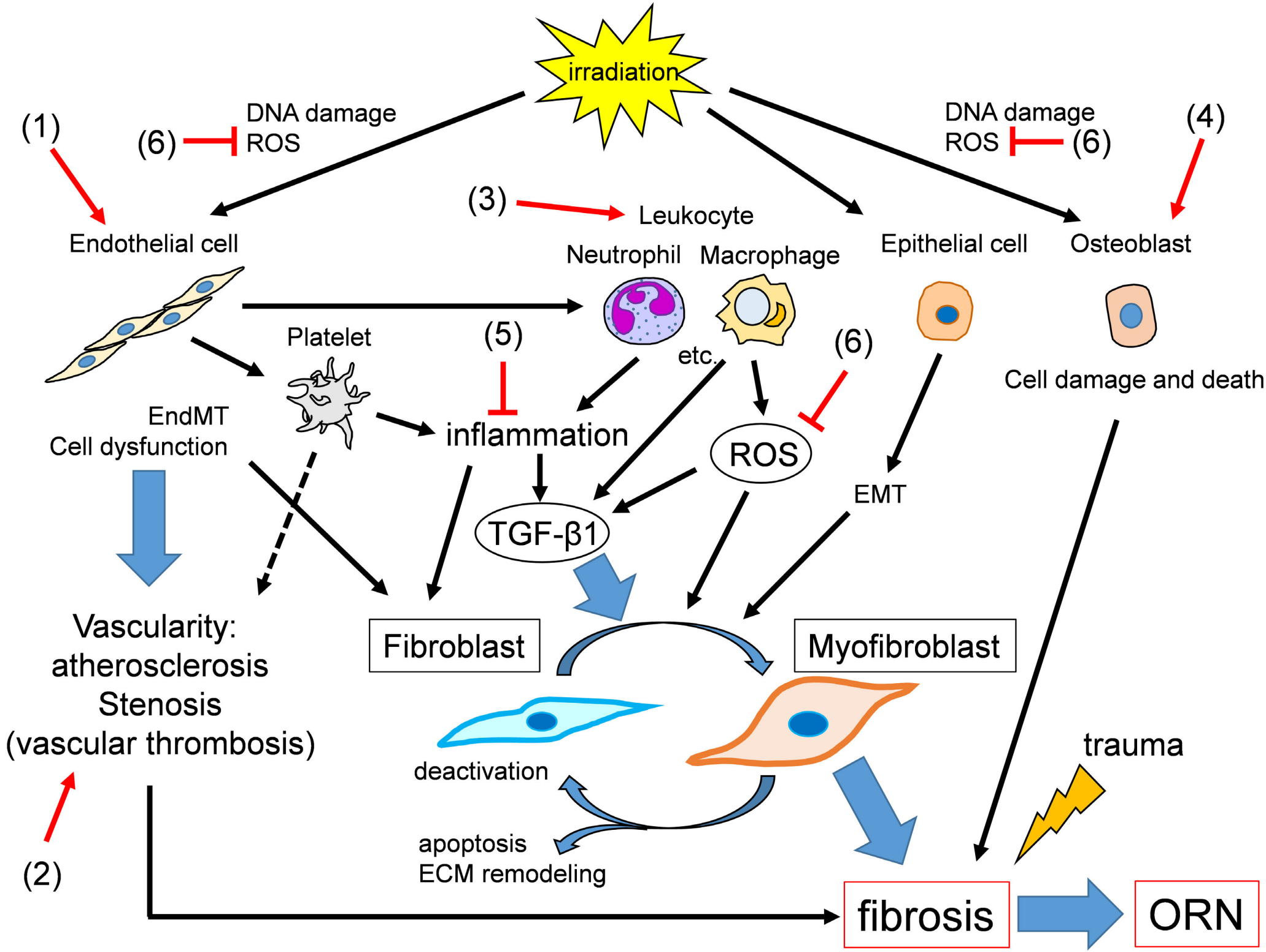


Number at risk							
Non-stage 1	51	28	13	8	4	3	2
Stage 1	51	25	6	4	1	1	1



Number at risk

No dyslipidemia	80	39	9	3	1	1
Non-statin treatment	10	7	4	1	1	1
Statin treatment	12	10	6	2	2	2


irradiation
(1)
(6)
DNA damage
ROS
DNA damage
ROS
(6)
(4)
(3)
Leukocyte
Endothelial cell
Neutrophil
Macrophage
Epithelial cell
Osteoblast
Platelet
(5)
etc.
(6)
Cell damage and death
EndMT
Cell dysfunction
inflammation
ROS
EMT
TGF-β1
Vascularity:
atherosclerosis
Stenosis
(vascular thrombosis)
Fibroblast
Myofibroblast
deactivation
trauma
apoptosis
ECM remodeling
(2)
fibrosis
ORN